DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 5, 206, 250, 314, 600, and 601

[Docket No. 99N–0193]

RIN 0910–AB61

Supplements and Other Changes to an Approved Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations on supplements and other changes to an approved application to implement the manufacturing changes provision of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The proposed rule would require manufacturers to validate the effect of any manufacturing change on the identity, strength, quality, purity, and potency of a drug or biological product as those factors relate to the safety or effectiveness of the product. The proposal sets forth requirements for changes requiring supplement submission and approval prior to the distribution of the product made using the change, changes requiring supplement submission at least 30 days prior to the distribution of the product, changes requiring supplement submission at the time of distribution, and changes to be described in an annual report.

DATES: Written comments by (*insert date 75 days after date of publication in the* **Federal Register**). Comments on the collection of information by (*insert date 30 days after date of publication in the* **Federal Register**).

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written

comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Introduction

On November 21, 1997, the President signed the Modernization Act (Pub. L. 105–115) into law. Section 116 of the Modernization Act amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 506A (21 U.S.C. 356a), which describes requirements and procedures for making and reporting manufacturing changes to approved new drug and abbreviated new drug applications, to new and abbreviated animal drug applications, and to license applications for biological products. This proposed rule sets forth regulations to implement section 506A of the act for human new drug and abbreviated new drug applications and for licensed biological products. The Center for Veterinary Medicine is developing separate regulations regarding manufacturing changes for new and abbreviated animal drug applications.

This proposed rule will update and replace current § 314.70 (21 CFR 314.70), which provides the requirements for manufacturing changes for human drug applications. This proposal also proposes changes to § 601.12 (21 CFR 601.12), which provides the requirements for manufacturing changes for licensed biological products. Although the current § 601.12 for licensed biological products is in full compliance with the new provisions in the Modernization Act, FDA is making the proposed changes in order to maintain harmonization with proposed § 314.70 for human drug applications.

II. Background

The requirements for reporting manufacturing changes under current § 314.70 were developed originally as part of a comprehensive effort to improve the investigational new drug application (IND) and the new drug application (NDA) processes. This effort began in October 1982 (47 FR 46622, October 19, 1982) and consisted of three phases. The first phase, termed the NDA rewrite (50 FR 7452, February 22, 1985), finalized procedures in part 314 (21 CFR part 314), including § 314.70, for FDA review of new drug and antibiotic applications. The NDA rewrite of § 314.70 created three mechanisms for reporting manufacturing changes: Supplements requiring prior approval, supplements not requiring prior approval, and annual reports. The rationale behind the need for three mechanisms to report manufacturing and controls changes is that some changes have a significant potential to affect the safety or effectiveness of a final drug product and should be reviewed and approved by FDA prior to distribution of the product made with the change. Other changes have a lesser potential to affect safety or effectiveness and could be implemented by a firm with notification to FDA concurrently (changes being effected supplement). A third category of changes has a minimal potential to affect safety or effectiveness and could, therefore, be submitted in the next annual report without compromising drug safety or effectiveness.

The second phase of the effort to improve the IND and NDA process, termed the IND rewrite (52 FR 8831, March 19, 1987), finalized FDA procedures in 21 CFR part 312 for reviewing IND's. The third phase involved preparation of a series of agency guidances that elaborated on the concepts contained in the IND and NDA regulations and provided more detail concerning application formats and how to fulfill testing and other regulatory requirements.

In implementing § 314.70, the agency recognized both the need for greater consistency in the approaches FDA recommended for application holders making postapproval manufacturing and controls changes as well as a need to reduce regulatory burden consistent with the public health. Accordingly, FDA formed the Scale-up and Postapproval Changes (SUPAC) Task Force. This SUPAC Task Force, which was established by the Center for Drug Evaluation and Research

(CDER) Chemistry, Manufacturing, and Controls Coordinating Committee, oversaw the acquisition of data on the effects of postapproval changes on the quality and performance of drugs. Based on the data and CDER's experience reviewing thousands of manufacturing change supplements, CDER developed guidance documents designed to ease preapproval requirements by categorizing certain manufacturing changes according to whether they had a minor, moderate, or major potential to affect product quality and performance. The SUPAC guidance documents were issued under § 314.70(a), which stated that holders of an approved application shall make changes to the application in accordance with a guideline, notice, or regulation published in the **Federal Register** that provides for a less burdensome notification of the change.

The existing postapproval change guidances are based on the concept that the identity, strength, quality, purity, and potency of an approved drug should remain unchanged in any important aspect as a result of any postapproval change in manufacturing and controls. A change in any important aspect may thus require redemonstration of pharmaceutical equivalence and/or bioequivalence as defined in 21 CFR 320.1.

Regulations governing manufacturing changes to licensed biological products were similar to § 314.70, although they did not include the three categories of changes provided in § 314.70. In 1997, as part of an agency initiative to reduce regulatory burden, FDA revised § 601.12 to add three categories of manufacturing changes for licensed biological products with different reporting requirements for each category. In addition, because certain biotechnology products were regulated as drugs under section 505 of the act (21 U.S.C. 355), FDA sought to harmonize regulatory approaches for those biotechnology products that were regulated as drugs by adding new § 314.70(g) that addressed reporting changes to an approved application for certain biotechnology products (see 61 FR 2739, January 29, 1996, and 62 FR 39890, July 24, 1997). Revised §§ 601.12 and 314.70(g), like the original § 314.70, provided for three risk-based filing categories: (1) Those having a substantial potential to have an adverse effect on the identity, strength, quality, purity, and potency of a drug as those factors relate to the safety or effectiveness of the product; (2)

those having a moderate potential to have these types of effects; and (3) those with minimal potential to have such effects. In addition, §§ 601.12 and 314.70(g) provided for four different reporting categories instead of the three originally provided in § 314.70. These categories were: (1) Prior approval supplement; (2) 30-day wait changes being effected supplement; (3) no-wait changes being effected supplement; and (4) annual report.

Sections 601.12 and 314.70(g) also provided that applicants could submit as a preapproval supplement a comparability protocol that described the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. If approved, such a protocol could justify a reduced reporting category for the particular change described because the use of the protocol for the change could reduce the potential risk of an adverse effect associated with the change.

III. Summary of the Legislation

Section 116 of the Modernization Act amended the act by adding section 506A, which built upon the concepts embodied in the IND/NDA rewrite, the SUPAC program, and the changes to §§ 601.12 and 314.70(g). Section 506A of the act includes the following provisions:

1. A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the applicant validates the effects of the change on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug (sections 506A(a)(1) and (b) of the act). This section recognizes that additional testing, beyond testing to ensure that an approved specification is met, is required to ensure unchanged identity, strength, quality, purity, or potency as these factors may relate to the safety or effectiveness of the drug.

2. A drug made with a major manufacturing change may be distributed only after the applicant submits a supplemental application to FDA and the supplemental application is approved by the agency. The application is required to contain information determined to be appropriate by FDA

and include the information developed by the applicant when ''validating the effects of the change'' (section 506A(c)(1) of the act). The phrase ''validating the effects of the change,'' as used in this proposed rule, is not the same as ''validation'' required in FDA's current good manufacturing practice (CGMP) regulations (parts 210 and 211 (21 CFR parts 210 and 211)). Unless otherwise specified by FDA, some CGMP validation (e.g., process, equipment) data need not be filed in an NDA, abbreviated new drug application (ANDA), or license application for a biological product but should be retained at the facility and be available for review by FDA at its discretion. Some other CGMP validation information, in addition to the information validating the effects of the change specified in section 506A(c)(1) of the act, should be submitted in an NDA, ANDA, or license application for a biological product (e.g., sterilization and advantageous agent removal process validation).

3. A major manufacturing change is a manufacturing change determined by FDA to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Such changes include: (1) A change made in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved application or license unless exempted by FDA by regulation or guidance; (2) a change determined by FDA by regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug manufactured without the change; and (3) other changes determined by FDA by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug (section 506A(c)(2) of the act).

4. FDA may require submission of a supplemental application for drugs made with manufacturing changes that are not major (section 506A(d)(1)(B) of the act) and establish categories of manufacturing changes for which a supplemental application is required (section 506A(d)(1)(C) of the act). In such a case the applicant may begin distribution of the drug 30 days after FDA receives a supplemental application unless the agency notifies the applicant within the 30-day period

that prior approval of the application is required (section 506A(d)(3)(B)(i) of the act). FDA may also designate a category of manufacturing changes that permit the applicant to begin distributing a drug made with such changes upon receipt by the agency of a supplemental application for the change (section 506A(d)(3)(B)(ii) of the act). If FDA disapproves a supplemental application, the agency may order the manufacturer to cease the distribution of drugs that have been made with the disapproved change (section 506A(d)(3)(B)(iii) of the act).

5. FDA may authorize applicants to distribute drugs without submitting a supplemental application (section 506A(d)(1)(A) of the act) and may establish categories of manufacturing changes that may be made without submitting a supplemental application (section 506A(d)(1)(C) of the act). The applicant is required to submit a report to FDA on such a change and the report is required to contain information the agency deems to be appropriate and information developed by the applicant when validating the effects of the change. FDA may also specify the date on which the report is to be submitted (section 506A(d)(2)(A) of the act). If during a single year an applicant makes more than one manufacturing change subject to an annual reporting requirement, FDA may authorize the applicant to submit a single report containing the required information for all the changes made during the year (annual report) (section 506A(d)(2)(B) of the act).

Section 506A of the act provides FDA with considerable flexibility to determine the information and filing mechanism required for the agency to assess the effect of manufacturing changes in the safety and effectiveness of the product. There is a corresponding need to retain such flexibility in the proposed regulations implementing section 506A of the act to ensure that the least burdensome means for reporting changes are available. FDA believes that such flexibility will allow it to be responsive to increasing knowledge of and experience with certain types of changes and help ensure the efficacy and safety of the products involved. For example, a change that may currently be considered to have a substantial potential to have an adverse effect on the safety or effectiveness of the product may, at a later date, based on new information or advances in technology, be determined to have a lesser potential to have such an adverse effect. Conversely,

a change originally considered to have a minimal or moderate potential to have an adverse effect on the safety or effectiveness of the product may later, as a result of new information, be found to have an increased, substantial potential to adversely affect the product.

The agency believes it can more readily respond to knowledge gained from manufacturing experience, further research and data collection, and advances in technology by issuing regulations that set out broad, general categories of manufacturing changes and by using guidance documents to provide FDA's current thinking on the specific changes that fall into those general categories. The proposed rule would, therefore, help reduce the number of manufacturing changes specifically identified as requiring supplements.

The agency also understands that applicants expect some predictability on what type of reporting will be expected for specific changes. FDA intends to make available guidance documents to describe the agency's current interpretation of specific changes falling into the four filing categories and to modify the documents as needed to reflect changes based on new information. Section 506A of the act explicitly provides FDA the authority to use guidance documents to determine the type of changes that do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug product. The use of guidance documents will allow FDA to more easily and quickly modify and update important information. (FDA's use of guidance documents under current §§ 314.70(a) and 601.12 has proven effective in accomplishing this goal.) Guidance documents will be developed according to the procedures set out in FDA's ''Good Guidance Practices'' published in the **Federal Register** of February 27, 1997 (62 FR 8961 at 8967 through 8972). A notice of availability of a draft guidance entitled ''Guidance for Industry: Changes to an Approved NDA or ANDA'' is published elsewhere in this issue of the **Federal Register**. This draft guidance covers recommended reporting categories for various postapproval manufacturing changes. Previously published guidances, including the SUPAC guidances, provide recommendations on reporting categories as well as the type of information that should be developed by the applicant to validate the effect of the change on the identity, strength, quality,

purity, or potency of a product as they may relate to the safety or effectiveness of the product. To the extent that the recommendations on reporting categories in this guidance, when finalized, are inconsistent with previously published guidance, such as the SUPAC guidances, the recommended reporting categories in such prior guidance will be superseded by this new guidance upon its publication in final form. CDER intends to update the previously published guidances to make them consistent with this guidance.

FDA has also published a guidance entitled ''Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products'' (62 FR 39904, July 24, 1997). FDA intends to update this guidance as appropriate based on any final rule that may issue as a result of this proposal.

IV. Description of the Proposed Rule

A. Definitions

FDA is proposing to amend the ''Definitions'' sections of the regulations on applications for FDA approval to market a new drug (§ 314.3) and a biological product (21 CFR 600.3) by adding definitions for ''specification'' and ''validate the effects of the change.'' These definitions are necessary to implement the provisions of section 506A of the act.

FDA is proposing to define ''specification'' as the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials. FDA is proposing to define ''specification'' because under section 506A of the act a ''major change'' includes a change ''in the specifications in the approved application or license.''

To clarify the meaning of the term ''acceptance criteria'' as used in the definition of ''specification,'' FDA is including in the proposed definition of ''specification'' the statement that ''acceptance criteria'' refers to numerical limits, ranges, or other criteria for the tests described.

To determine if a material being tested complies with a specification, there must be predetermined criteria. These criteria may include numerical limits or ranges (e.g., not more than 1 percent) or other criteria (e.g., white to off-white in color).

FDA is proposing to define ''validate the effects of the change'' as an assessment of the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug. FDA is proposing to define this phrase because section 506A of the act includes a requirement that a drug made with a manufacturing change may only be distributed after the applicant ''validates the effects of the change.'' Validating the effects of the change is important in determining whether manufacturing changes alter the identity, strength, quality, purity, or potency of a drug product as they relate to drug safety or effectiveness, and may require testing beyond that in an approved specification, such as testing to ensure pharmaceutical equivalence and/or bioequivalence.

B. Changes to an Approved Application

Current § 314.70(a) sets forth general requirements under which an applicant must notify FDA when making a change to an approved application. This section states that an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application, and that the notice is required to describe the change fully. It also states that, depending on the type of change, the applicant must notify FDA of it in a supplement under current § 314.70(b) or (c) or by inclusion of the information in an annual report under current § 314.70(d). FDA is proposing to retain these general requirements under proposed § 314.70(a)(1). A similar provision is included in the regulations on changes to an approved application for biological products under current § 601.12(a). FDA is proposing to redesignate this requirement as § 601.12(a)(1).

Proposed § 314.70(a)(2) would require the holder of an approved application under section 505 of the act to validate the effects of manufacturing changes on the identity, strength (e.g., assay and content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g.,

impurities and degradation products) or potency (e.g., biological activity, bioavailability, and bioequivalence) of a drug as these factors may relate to the safety and effectiveness of the drug. These validation requirements must be met before a product made with a manufacturing change may be distributed. This amendment implements section 506A(a)(1) and (b) of the act. A similar provision is included in the regulations on changes to an approved application for biological products under current § 601.12(a). FDA is proposing to add minor wording changes for consistency with revised § 314.70 and to redesignate this requirement as § 601.12(a)(2). In addition, applicants continue to be subject to the validation requirements of parts 210 and 211 as mentioned previously.

Current § 314.70(a) states that notwithstanding the supplement submission requirements of current § 314.70(b) and (c), an applicant shall make a manufacturing change in accordance with ''a guideline, notice, or regulation published in the **Federal Register** that provides for a less burdensome notification of the change.'' For example, a type of manufacturing change subject to prior approval by FDA under current § 314.70(b) might be identified in a ''guideline, notice, or regulation'' as a change that could be reported in a supplement not requiring prior approval or in an annual report. In the SUPAC guidance documents, CDER used this provision to reduce the regulatory burden for submission of supplements for manufacturing changes that were not likely to adversely affect drug product quality or performance.

FDA is proposing to retain this requirement under proposed § 314.70(a)(3) and to add it to the regulations on changes to an approved application for biological products as proposed § 601.12(a)(3). This exception may be used as pharmaceutical science evolves for those changes that FDA no longer considers to have a substantial potential to have an adverse effect on the product. However, to ensure consistency with the principles of FDA's good guidance practices, proposed §§ 314.70(a)(3) and 601.12(a)(3) would eliminate the reference to a **Federal Register** ''notice'' and change the word ''guideline'' to ''guidance.'' Proposed § 314.70(a)(3) is expressly sanctioned in section 506A(c)(2)(A), (c)(2)(B), and (c)(2)(C) of the act which permit FDA to categorize manufacturing changes ''by regulation or guidance.''

Current § 314.70(c) states, in the introductory paragraph, that the applicant who submits a change being effected supplement to FDA must promptly revise all promotional labeling and drug advertising to make it consistent with any change in the labeling. FDA is proposing to retain this provision as proposed § 314.70(a)(4) and to add it to the regulations on changes to an approved application for biological products as proposed § 601.12(a)(4). Because the prompt revision of all promotional labeling and product advertising applies equally to all labeling changes (see § 314.81(b)(3)), FDA is proposing that this provision expressly apply to labeling changes requiring approval prior to the distribution of the product, labeling changes that may be submitted in a changes being effected supplement, and those changes that may be filed in an annual report.

Current § 314.70(a) also requires that, except for a supplemental application providing for a change in the labeling, the applicant, other than a foreign applicant, shall include in each supplemental application providing for a change under paragraph (b) or (c) of current § 314.70, a statement certifying that a field copy of the supplement has been provided to the applicant's home FDA district office. FDA is proposing to retain this requirement as proposed § 314.70(a)(5). However, as proposed, this section would omit the phrase ''other than a foreign applicant'' because foreign applicants now routinely supply field copies of supplements to the agency.

Proposed §§ 314.70(a)(6) and 601.12(a)(5) would add a requirement that a list of all changes contained in the supplement or annual report must be included in the cover letter for the supplement or annual report. For many years, most supplements and annual reports have routinely included such cover letters. Including a list of all changes in the cover letters will enable FDA to more efficiently locate and evaluate changes in what are often substantial documents, thus facilitating FDA review of supplements and annual reports.

C. Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes)

Certain drug or biological product manufacturing steps are so critical that changes in these steps must be submitted in a supplement to FDA and approved by FDA prior to distribution of

the product made using the change. Similarly, certain labeling changes must be approved prior to distribution of the product with the new labeling. Current regulations at §§ 314.70(b) and (g)(1) and 601.12(b) set forth prior approval requirements. FDA is proposing to revise these regulations to implement section 506A of the act. Proposed § 314.70(b)(1) would implement section 506A(c)(1) and (c)(2) of the act and would require that a preapproval supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product.

Sometimes, during assessment of a change, an applicant will find that the manufacturing change will have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant will not implement this manufacturing change, but in some cases may still wish to do so. If an assessment concludes that a manufacturing change has adversely affected the identity, strength, quality, purity, or potency of the drug product, the change should be filed in a prior approval supplement, regardless of whether the change is one that normally does not need FDA approval prior to distribution of the product made with the change. The applicant could submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. The agency will assess the effect of any adverse change in a drug product, as the change may relate to the safety or effectiveness of the product, during the review of the prior approval supplement.

Proposed § 314.70(b)(4) would retain the provision in current § 314.70(b) that provides that an applicant may request an expedited review of a supplement if a delay in making the change would impose an extraordinary hardship. Proposed § 314.70(b)(4) would also permit a request for an expedited review of a supplement for public health reasons. FDA is retaining the provision for expedited review for extraordinary hardship reasons but wishes to clarify that these requests should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

FDA is also proposing to add this provision for expedited review, as proposed in § 314.70(b)(4), to the regulations on changes to an approved application for biological products as proposed § 601.12(b)(4). Requests for expedited review will be assessed on a case-by-case basis. All requests may not be granted.

Proposed § 314.70(b)(2) lists changes requiring supplement submission and FDA approval prior to distribution, including changes designated as major manufacturing changes in section 506A(c)(2) of the act and changes to certain biotechnology products that are currently subject to prior approval requirements under current § 314.70(g)(1). These changes have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. The agency believes that the filing mechanism for these significant changes is unlikely to vary with technological advances or due to differences among products, and that these changes should be enumerated in the proposed regulations. The agency's continued prior review and approval of such changes is necessary to protect the public from products for which safety or effectiveness may have been compromised. The changes in proposed § 314.70(b)(2) would include but are not limited to the following changes.

1. Changes in the qualitative or quantitative formulation of the drug, including inactive ingredients, or in the specifications in the approved application or license, except as provided in proposed § 314.70(c) and (d) (proposed § 314.70(b)(2)(i)). Section 506A(c)(2)(A) of the act specifically requires that this change be submitted in a supplement requiring FDA approval prior to distribution. These types of changes are included under current § 314.70(b) and (g) as requiring a prior approval supplement. FDA is also proposing to revise current § 601.12(b)(2)(i) in the regulations on changes to an approved application for biological products to be consistent with proposed § 314.70(b)(2)(i).

2. Changes requiring completion of studies in accordance with part 320 (21 CFR part 320) to demonstrate the equivalence of the drug to the drug as manufactured without the change or to the reference listed drug (proposed § 314.70(b)(2)(ii)). A similar change is included under current

§ 314.70(g)(1) as requiring a prior approval supplement. FDA is proposing that these changes be submitted in a supplement requiring prior approval because section 506A of the act provides that a major manufacturing change shall include a change ''determined by the Secretary by regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug as manufactured without the change''(section 506A(c)(2)(B) of the act). The studies most likely to be conducted to support a manufacturing change would be bioavailability or bioequivalence studies conducted in humans in accordance with FDA regulations at part 320. Well-controlled clinical trials or nonclinical tests may also be used to establish bioavailability or bioequivalence (§ 320.24). These are the types of studies the statute refers to as demonstrating the equivalence of one drug to another. FDA proposes interpreting ''Appropriate clinical stud[ies],'' referenced in section 506A(c)(2)(B) of the act for NDA products, to be ''studies in accordance with part 320 of this chapter'' to clarify the types of studies triggering a prior approval supplement. This phrase is used in the proposed regulation at § 314.70(b)(2)(ii).

Section 506A of the act also states in part that ''equivalence of the drug to the drug as manufactured without the change'' should be demonstrated. FDA is including in proposed § 314.70(b)(2)(ii) the statement that the equivalence of the drug may sometimes be demonstrated by comparison to a reference listed drug. This is consistent with the drug approval requirements for generic drugs because, at the time of approval, a generic drug applicant is required to show equivalence between the proposed generic drug and a reference listed drug, and a proposed manufacturing change should not significantly change the equivalence demonstrated at the time of approval (§ 320.21(b)). For the more significant manufacturing changes for generic drugs, the applicant is required to conduct a bioequivalence study comparing the drug product made with the change to the reference listed drug. FDA is not proposing the same changes to § 601.12 because biological products are not subject to part 320 and have unique properties. Therefore, the agency will retain the wording in current § 601.12(b)(2)(ii).

3. Changes that may affect product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation (proposed § 314.70(b)(2)(iii)). Current §§ 314.70(g)(1) and 601.12(b)(2)(vi) require a prior approval supplement for this change.

4. Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance (proposed § 314.70(b)(2)(iv)). A similar change in current § 314.70(b)(1) requires a prior approval supplement.

5. Changes in labeling, except those described in proposed § 314.70(c)(6)(iii) (changes to add or strengthen certain warnings or statements), § 314.70(d)(2)(ix) (certain changes in the description or information about a drug), and § 314.70(d)(2)(x) (certain editorial or minor changes) (proposed § 314.70(b)(2)(v)). This change requires a prior approval supplement under current § 314.70(b)(3).

6. Changes in a container closure system that controls drug delivery or that may affect the impurity profile of the drug product (proposed § 314.70(b)(2)(vi)). Significant changes in container closure systems require a prior approval supplement under current § 314.70(b)(2).

7. Changes solely affecting a natural product, a recombinant deoxyribonucleic acid (DNA)-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody for: (1) Changes in the virus or adventitious agent removal or inactivation method(s); (2) changes in the source material or cell line; and (3) establishment of a new master cell bank or seed (proposed § 314.70(b)(2)(vii)). This change requires a prior approval supplement under current § 314.70(g)(1).

8. Changes to a product under an application subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application (proposed § 314.70(b)(2)(viii)). Until questions about the integrity of the data in the application have been resolved, there are inadequate assurances that any change will not adversely affect the safety or effectiveness of the product. Moreover, a change to a product cannot be validated, as required under 506A(b) of the act, until the integrity of the underlying data in such application is validated.

Consequently, there is a significant potential that the change will have an adverse effect on the identity, strength, quality, purity, or potency of the product. After a validity assessment has been completed, and data integrity questions resolved, the holder of an approved application may submit supplements for manufacturing changes as otherwise provided in § 314.70.

FDA is proposing to describe additional specific examples of changes that have substantial, moderate, and minimal potential to adversely affect a product in guidance documents rather than enumerate them in this proposed regulation. As discussed previously, section 116 of the Modernization Act expressly states that the agency may through guidance categorize the manufacturing changes. FDA anticipates that scientific advances and future experience may reduce the need for premarket approval of certain changes, and the agency will respond to changed circumstances by revising the guidance documents. A notice of availability of a draft guidance document entitled ''Guidance for Industry: Changes to an Approved NDA or ANDA'' that provides more detailed recommendations on how to report proposed changes is being published elsewhere in this issue of the **Federal Register**, and the agency is soliciting comments on the guidance as well as on the proposed rule.

Current § 314.70(b)(1) requires that supplements requiring prior approval be submitted for the following changes in a drug substance: (1) Relaxing the limits for a specification (§ 314.70(b)(1)(i)); (2) establishing a new regulatory analytical method (§ 314.70(b)(1)(ii)); (3) deleting a specification or regulatory analytical method (§ 314.70(b)(1)(iii)); (4) changing the synthesis of the drug substance, including a change in solvents and a change in the route of synthesis (§ 314.70(b)(1)(iv)); and (5) using a different facility or establishment to manufacture the drug substance (§ 314.70(b)(1)(v)). FDA is proposing to revoke current § 314.70(b)(1)(i), (b)(1)(ii), and (b)(1)(iii) because these relate to a change in a specification which is already covered under proposed § 314.70(b)(1). FDA is proposing to revoke current § 314.70(b)(1)(iv) and (b)(1)(v) because some of these changes would fall into the proposed major manufacturing change category while others would fall into other proposed categories depending on whether the change is

considered to have a substantial, moderate, or minimal potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of the drug. FDA has decided not to include these changes in this proposed rule, but plans to provide recommendations on the filing mechanisms for these types of changes in the guidance documents discussed previously.

Current § 314.70(b)(2) requires that supplements requiring prior approval be submitted for the following changes in a drug product: (1) Adding or deleting an ingredient, or otherwise changing the composition of the drug product, other than deletion of an ingredient intended only to affect the color of the drug product (§ 314.70(b)(2)(i)); (2) relaxing the limits for a specification (§ 314.70(b)(2)(ii)); (3) establishing a new regulatory analytical method (§ 314.70(b)(2)(iii)); (4) deleting a specification or regulatory analytical method (§ 314.70(b)(2)(iv)); (5) changing the method of manufacture of the drug product, including changing or relaxing an in-process control (§ 314.70(b)(2)(v)); (6) using a different facility or establishment, including a different contract laboratory or labeler, to manufacture, process, or pack the drug product (§ 314.70(b)(2)(vi)); (7) changing the container and closure system for the drug product or changing a specification or regulatory analytical method for the container and closure system (§ 314.70(b)(2)(vii)); (8) changing the size of the container, except for solid dosage forms, without a change in the container and closure system (§ 314.70(b)(2)(viii)); (9) extending the expiration date of the drug product based on data obtained under a new or revised stability testing protocol that has not been approved in the application (§ 314.70(b)(2)(ix)); (10) establishing a new procedure for reprocessing a batch of the drug product that fails to meet specifications (§ 314.70(b)(2)(x)); (11) adding a code imprint by printing with ink on a solid oral dosage form drug product (§ 314.70(b)(2)(xi)); (12) adding a code imprint by embossing, debossing, or engraving on a modified release solid oral dosage form drug product (§ 314.70(b)(2)(xii)). FDA is proposing to revoke § 314.70(b)(2)(i) through (b)(2)(iv) because these provisions relate to a change in qualitative or quantitative formulation or a specification that is already covered under proposed § 314.70(b)(1). FDA is proposing to revoke

current § 314.70(b)(2)(v) through (b)(2)(xii) because some changes would fall into the proposed major manufacturing changes category while others would fall into other proposed categories. FDA plans to provide recommendations on the filing mechanism for these changes in the guidance documents discussed previously.

Proposed § 314.70(b)(3) states that the applicant must obtain approval of a supplement from FDA before distributing a product using a change under § 314.70(b), and specifies information to be included in the supplement. The supplement must include: (1) A detailed description of the proposed change; (2) the product(s) involved; (3) the manufacturing site(s) or area(s) affected; (4) a description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validating the effects of the change); (5) data derived from such studies; (6) for a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody, relevant validation protocols must be provided in addition to the requirements under § 314.70(b)(3)(iv) and (b)(3)(v); (7) for sterilization process and test methodologies, relevant validation protocols must be provided in addition to the requirements under § 314.70(b)(3)(iv) and (b)(3)(v); and (8) if applicable, a reference list of relevant standard operating procedures (SOP's). These supplement content requirements are already required under current §§ 314.70(g)(1)(iii) and 601.12(b)(3), and FDA is proposing to retain the requirements in this rule, except that the proposal specifies that relevant validation protocols and data apply to a natural product, a recombinant DNA-derived protein/ polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody, as well as protocols and data for sterilization processes and test methodologies.

Current § 314.70(g)(1)(iii) only applies to recombinant DNA-derived protein/polypeptide products or complexes or conjugates of a drug with a monoclonal antibody. Some information requirements listed under current § 314.70(g)(1)(iii) are not applicable to all CDER drug products.

FDA is proposing to clarify the requirements in current § 314.70(g)(1)(iii) to describe the limited circumstances under which certain information would be required.

D. Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Changes)

Current § 314.70(c) describes changes that may be made before FDA approval of a supplement. These include changes to enhance the safe use of a drug by adding specifications to strengthen warnings, or to delete false, misleading, or unsupported indications for use. Current § 314.70(g)(2) describes changes requiring supplement submission at least 30 days prior to distribution of the product made using the change. These include changes in the site of testing from one facility to another, an increase or decrease in production scale during finishing steps that involves new or different equipment, and replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters. FDA recognizes that the public health can be adequately protected without requiring approval of certain manufacturing changes prior to distribution of the product made with the change. FDA continues to believe that it is important that such changes be documented and validated so there is a mechanism for assessing the consequences of the change and that the agency approve such changes. Ready access to information regarding such changes through submission of a supplement 30 days before distribution of the product would protect against the distribution of unsafe or ineffective products while speeding the availability of improved products.

Proposed § 314.70(c) implements section 506A(d)(1)(B) and (d)(3)(B)(i) of the act and provides that products made using changes listed under this section may be distributed not sooner than 30 days after receipt of a supplement by FDA. Proposed § 314.70(c)(1) would require that a supplement be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. Proposed § 314.70(c)(3) states that a supplement submitted under

paragraph (c)(1) is required to give a full explanation of the basis for the change and identify the date on which the change is to be made, and that the supplement must be labeled ''Supplement—Changes Being Effected in 30 Days'' or, if applicable under paragraph (c)(6) of this section, ''Supplement—Changes Being Effected.''

Proposed § 314.70(c)(2) describes the types of changes that would be included under this section:

1. A change in the container closure system that does not affect the quality of the final drug product (proposed § 314.70(c)(2)(i)).

2. Changes solely affecting a natural protein product, a recombinant DNA-derived protein/ polypeptide product or a complex or conjugate of a drug with a monoclonal antibody, including: (1) An increase or decrease in production scale during finishing steps that involves new or different equipment and (2) replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters (proposed § 314.70(c)(2)(ii)). These changes are listed in current § 314.70(g)(2) as requiring the submission of a supplement at least 30 days prior to distribution.

Current § 314.70(g)(2) lists a change in the site of testing from one facility to another as a change that must be filed in a supplement submitted at least 30 days prior to distribution. FDA has decided not to include a similar change in proposed § 314.70(c) and is proposing to delete this change from current § 601.12(c)(2)(i). FDA plans to provide recommendations on the filing mechanism for this change in the guidance documents discussed previously.

Proposed § 314.70(c)(4) states that distribution of a product made using a change under this section may begin not less than 30 days after receipt of a supplement by FDA. This section would also require that the same information listed in paragraph (b)(3), discussed previously, must be contained in the supplement required under proposed § 314.70(c).

Proposed § 314.70(c)(5) states that during the 30-day period following receipt of the supplement, FDA would perform a preliminary review to determine whether the supplement is

complete and whether the type of change is appropriate for review as a supplement under proposed § 314.70(c). If the proposed change is determined to be a major change that should be submitted under proposed § 314.70(b), the agency would inform the applicant and the applicant would be required to receive FDA approval before a product produced with the change could be distributed. If FDA determines that the change is properly submitted as a supplement under § 314.70(c), but the required information is incomplete, the applicant would be required to supply the missing information and wait until FDA has determined that the supplement is in compliance before distributing the product. These provisions are provided in section 506A(d)(3) of the act. These requirements are included under current §§ 314.70(g)(2)(iv) and 601.12(c)(4) and FDA is retaining and expanding this requirement to cover all drugs.

Under proposed § 314.70(c)(7), if FDA disapproves a supplemental application under this section, the agency may order the manufacturer to cease distribution of the drug products made with the manufacturing change. This amendment would implement section 506A(d)(3)(B)(iii) of the act. FDA is also proposing to add this provision to the regulations on changes to an approved application for biological products as proposed § 601.12(c)(6).

E. Changes That May Be Implemented When FDA Receives a Supplement (Moderate Changes)

Under proposed § 314.70(c)(6), FDA may designate a category of changes for which the holder of an approved application making such a change may begin distribution of the drug upon receipt by FDA of a supplemental application for the change. This provision implements section 506A(d)(3)(B)(ii) of the act. FDA recognizes that the public health can be adequately protected without requiring approval of certain manufacturing changes prior to distribution of the product made with the change. FDA continues to believe that it is important that such changes be documented and validated so there is a mechanism for assessing the consequences of the changes and for the agency to approve such changes. However, based on FDA's experience, certain changes may be implemented when FDA receives the supplement, rather than delaying distribution for 30 days. In general, these changes provide the same or increased assurance that the product will have

the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to have. Ready access to information by FDA regarding such changes, through the submission of a supplement, would protect against the distribution of unsafe or ineffective products while speeding the availability of improved products.

These changes include, but are not limited to:

1. The addition to a specification or changes in the methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess (proposed § 314.70(c)(6)(i)). A similar change is listed under current § 314.70(c). Proposed § 314.70(c)(6)(i) revises current § 314.70(c) to provide clarification based on the proposed definition of specification and to delete the reference to facilities. FDA plans to provide recommendations on the filing mechanism for facility changes in the guidance documents discussed previously.

2. A change in the size and/or shape of a container (containing the same labeled amount of product) for a nonsterile drug product, except for solid dosage forms, without a change from one container closure system to another (proposed § 314.70(c)(6)(ii)). A similar change is listed under current § 314.70(b) as requiring prior approval. The proposal differs from the existing rule in that it only applies to nonsterile drug products, thereby reducing the potential risks and eliminating the need for a prior approval requirement. FDA is also clarifying that changes in container size relate to changes in the physical size of the container and do not include changes in the labeled amount of the drug.

3. Changes in the labeling to add or strengthen a contraindication, warning, precaution, or adverse reaction, or to add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage, or to add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product (proposed § 314.70(c)(6)(iii)(A), (c)(6)(iii)(B), and (c)(6)(iii)(C)). These changes are required under current § 314.70(c)(2), except that FDA is

proposing to include labeling changes relating to adding or strengthening a statement about psychological effects to maintain consistency with current § 601.12(f)(2)(B).

4. The deletion of false, misleading, or unsupported indications for use or claims for effectiveness (proposed § 314.70(c)(6)(iii)(D)). This change is required under current § 314.70(c)(2).

5. Any other labeling changes specifically requested by FDA (proposed § 314.70(c)(6)(iii)(E)). FDA is proposing to include this change under this section to enable the agency to allow for labeling changes that normally require prior approval to be submitted in a changes being effected supplement when FDA specifically requests the change. FDA is also proposing to add this requirement to the regulations on changes to an approved application for biological products as proposed § 601.12(f)(2)(i)(E).

Current § 314.70(c)(3) lists the following changes to use a different facility or establishment to manufacture the drug substance that may be made before FDA approval: (1) Where the manufacturing process in the new facility or establishment does not differ materially from that in the former facility or establishment, and (2) where the new facility or establishment has received a satisfactory CGMP inspection within the previous 2 years covering that manufacturing process. FDA is proposing not to include these changes in this proposed rule but plans to provide recommendations on the filing mechanism for these changes in the guidance documents discussed previously.

F. Changes To Be Described in the Next Annual Report (Minor Changes)

Proposed § 314.70(d) would provide that changes to the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product would be documented by the applicant in the next annual report in accordance with current § 314.81(b)(2). This provision is provided in section 506A(d)(2) of the act. FDA recognizes that there are manufacturing changes that have minimal potential to have an adverse effect on a product's safety or effectiveness. FDA believes that prior agency approval

of these changes is unnecessary and is proposing in § 314.70(d) that such changes would not be required to be approved by the agency. FDA continues to believe that it is important that such changes be documented and validated so there is a mechanism for assessing the consequences of the change. FDA can effectively assess compliance with § 314.70(d) and CGMP requirements for changes that have a minimal potential to adversely affect the product's safety or effectiveness by having ready access to information regarding such changes through submission of an annual report and by inspection.

Under proposed § 314.70(d)(2), these changes would include, but are not limited to:

1. Any change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess (proposed § 314.70(d)(2)(i)). Similar changes are listed in current § 314.70(d) and (g) as changes to be described in the next annual report. FDA is limiting the situations in which these changes can be submitted in an annual report because certain changes in a specification (e.g., deleting a test, relaxing acceptance criteria) are not considered to have minimal potential to effect a product's safety or effectiveness. FDA is also proposing to revise current § 601.12(d)(2)(i) in the regulations on changes to an approved application for biological products to be consistent with proposed § 314.70(d)(2)(i).

2. The deletion or reduction of an ingredient intended only to affect the color of the product (proposed § 314.70(d)(2)(ii)). A similar change is listed in current § 314.70(d) and (g)(3) which states that the deletion of an ingredient intended only to affect the color of the drug product should be submitted in an annual report. FDA is proposing to broaden this provision to include changes that reduce the quantity of an ingredient intended only to affect the color of the product. FDA is also proposing to revise current § 601.12(d)(2)(ii) in the regulations on changes to an approved application for biological products to be consistent with proposed § 314.70(d)(2)(ii).

3. The replacement of equipment with that of the same design and operating principles except for equipment used with a natural protein product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody (proposed § 314.70(d)(2)(iii)). FDA is proposing to add this change to clarify when certain changes in equipment could be reported in an annual report. In general, under current regulations (e.g., § 314.70(b)(2)(v)), changes in process, which may include changes in equipment, require a prior approval supplement and this proposal would reduce the regulatory burden without adversely affecting the quality of the drug product.

4. A change in the size and/or shape of a container containing the same number of dose units for a nonsterile solid dosage form, without a change from one container closure system to another (proposed § 314.70(d)(2)(iv)). A similar change is listed in current § 314.70(d) and (g)(3) which states that a change in the size of a container for a solid dosage form without a change from one container and closure system to another must be filed in an annual report. FDA is proposing to broaden this provision to include a change in the shape of the container. FDA is also clarifying that a change in container size relates to a change in the physical size of the container and does not include a change involving the number of dosage units. FDA is also proposing to revise current § 601.12(d)(2)(v) in the regulations on changes to an approved application for biological products to be consistent with proposed § 314.70(d)(2)(iv).

5. A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium (proposed § 314.70(d)(2)(v)). A similar change is listed in current § 314.70(d) and (g)(3) which states that a change within the container and closure system for the drug product (for example, a change from one high density polyethylene (HDPE) to another HDPE), except a change in container size for nonsolid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium, should be submitted in an annual report. The current regulations limit

this provision by excluding a change in container size for nonsolid dosage forms. FDA is proposing to broaden this provision to allow such changes for all nonsterile drug products. FDA is also proposing to revise current § 601.12(d)(2)(iv) in the regulations on changes to an approved application for biological products to be consistent with proposed § 314.70(d)(2)(v).

6. An extension of an expiration dating period based upon full shelf life data on full production batches obtained from a protocol approved in the application (proposed § 314.70(d)(2)(vi)). A similar change is listed under current § 314.70(d) and (g)(3) as one to be filed in an annual report. FDA is clarifying that the extension of an expiration date in an annual report should be based on data from full production batches. FDA is also proposing to revise current § 601.12(d)(2)(iii) regarding changes to an approved application for biological products to be consistent with proposed § 314.70(d)(2)(vi).

7. The addition, deletion, or revision of an alternate analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application (proposed § 314.70(d)(2)(vii)). A similar change is listed in current § 314.70(d) and (g)(3) which state that the addition or deletion of an alternate analytical method should be filed in an annual report. FDA is proposing to broaden this provision to include revisions of alternate analytical procedures. FDA is also clarifying that any changes in alternate analytical procedures should provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application. FDA is also proposing to revise current § 601.12(d)(2)(vii) in the regulations on changes to an approved application for biological products to be consistent with proposed § 314.70(d)(2)(vii).

8. The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint (proposed § 314.70(d)(2)(viii)). These changes are listed in current § 314.70(d) and (g)(3) as changes to be described in the next annual report.

9. A change in the labeling concerning the description of the drug product or in the information about how the drug is supplied, that does not involve a change in the dosage strength or dosage form (proposed § 314.70(d)(2)(ix)). These changes are listed in current § 314.70(d) as changes to be described in the next annual report.

10. An editorial or similar minor change in labeling (proposed § 314.70(d)(2)(x)). These changes are listed in current § 314.70(d) as changes to be described in the next annual report.

Under proposed § 314.70(d)(3), an applicant must submit in the annual report a list of all products involved and: (1) A statement by the holder of the approved application that the effects of the change have been validated; (2) a full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved; and (3) the date each change was made, a cross-reference to relevant validation protocol(s) and/or SOP's, and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validating the effects of the change). FDA is also proposing to revise current § 601.12(d)(3) in the regulations on changes to an approved application for biological products to add, as proposed § 601.12(d)(3)(iii), the requirement that the applicant must submit a statement that the effects of the change have been validated.

G. Other Information

Under proposed § 314.70(e), an applicant may submit one or more protocols describing specific tests, validation studies, and acceptable limits to be achieved to demonstrate the lack of an adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Such protocols, or changes to a protocol, would be submitted as a supplement requiring prior approval from FDA prior to distribution of the drug. If the supplement is approved, the use of such a protocol in making the specified changes may justify a reduced reporting category for the change because

of the reduced risk of an adverse effect. This proposed requirement is provided for in current §§ 314.70(g)(4) and 601.12(e).

Generally, when considering a change in the manufacture of a product, the manufacturer will prepare a protocol, often called a ''comparability protocol,'' identifying tests to be performed in evaluating the change and its effect on the product and defining the criteria against which the impact of the change will be evaluated. By providing FDA an opportunity to review and approve the comparability protocol before it is used by the applicant to evaluate a change, FDA can have greater assurance that the change is being properly evaluated and there is, therefore, less potential for the change to have an adverse effect on the safety or effectiveness of the product.

Under proposed § 314.70(f), an applicant would be required to comply with the patent information requirements under section 505(c)(2) of the act. This proposed requirement is identical to the current requirement at § 314.70(e).

Proposed § 314.70(g) would require an applicant claiming exclusivity under § 314.108 to include, with the supplemental application, information required under § 314.50(j). This proposed requirement is identical to the current requirement at § 314.70(f).

In addition to section 506A of the act, other sections of the act authorize FDA to revise §§ 314.70 and 601.12. Sections 301 and 501 of the act (21 U.S.C. 331 and 351) prohibit the manufacture, processing, packing, or holding of drugs that do not conform to CGMP; the use of unsafe color additives in or on a drug under section 721 of the act (21 U.S.C. 379e); and the distribution of a drug that differs in the strength, purity, or quality that it purports or is represented to possess. Sections 301 and 502 of the act (21 U.S.C. 352) prohibit false or misleading labeling of drugs, including, under section 201(n) of the act (21 U.S.C. 321(n)), failure to reveal material facts relating to potential consequences under customary conditions of use; drugs that lack adequate directions for use and adequate warnings; and the distribution of drugs that are dangerous to health when used in the manner suggested in their labeling. Under section 505 of the act, FDA will approve an NDA if the drug is shown to be safe and effective for its intended

use and if, among other things, the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the drug are adequate to preserve its identity, strength, quality, and purity. Section 701 of the act (21 U.S.C. 371) authorizes FDA to issue regulations for the efficient enforcement of the act.

The Public Health Service Act (the PHS Act) provides additional authority for FDA to revise § 601.12. Section 351(a) of the PHS Act (42 U.S.C. 262(a)) provides that license applications for biological products may be approved upon a showing that the product is safe, pure, and potent and that the manufacturing facility meets standards designed to ensure continued safety, purity, and potency of the product. In addition, under section 351(b) of the PHS Act, biological products and their containers or packages may not be falsely labeled or marked.

V. Conforming Amendments

The regulations on supplements and changes to an approved application or license are cited throughout FDA's regulations. Because FDA is proposing to revise these regulations, the agency is taking this opportunity to make conforming amendments to 21 CFR parts 5, 206, 250, 314, 600, and 601 to reflect these proposed regulations. These conforming amendments will ensure the accuracy and consistency of the regulations.

VI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the

economy, competition, or jobs. Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act (in section 202) requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in these two statutes. As shown in the following paragraphs, the rule will not be significant as defined by the Executive Order and the Unfunded Mandates Reform Act, and the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The purpose of the proposed rule is to implement section 506A of the act and to reduce the number of manufacturing changes subject to supplements requiring FDA approval prior to product distribution. The proposed rule would affect all drug manufacturers that submit manufacturing supplements and would result in a substantial reduction in burdens to applicants making manufacturing changes subject to the proposed regulation. The proposed rule would permit earlier implementation of the changes and quicker marketing of products improved by manufacturing or labeling modifications. Faster implementation can result in marked gains in production efficiency, and generally reduces the paperwork burden associated with reporting the changes to the agency. For example, a report by the Eastern Research Group (ERG), an FDA contractor, on the effects of the SUPAC guidance for immediate release solid oral dosage forms (SUPAC–IR) found that reducing the number of changes that require preapproval gives companies greater control over their production resources, which could lead to significant net savings to industry (Eastern Research Group, *Pharmaceutical Industry Cost Savings Through Use of the Scale-Up and Post-Approval Guidance for Immediate Release Solid Oral Dosage Forms (SUPAC–IR)*,

January 7, 1998, Contract No. 223–94–8301). Such economic incentives may encourage manufacturers to improve their products, product labeling, and methods of manufacture.

Due to the multiplicity of products and manufacturing changes, the agency has not estimated the total savings to industry as a result of this rule, but anticipates that they would increase over time. New information and technology will allow a greater number of changes to be reported in supplements that do not require prior approval or in annual reports. ERG estimated that companies may already have saved $71 million in 1997 due to the agency's implementation of more flexible reporting procedures for chemistry, manufacturing, and control changes. This proposed rule would broaden the potential scope of such savings. Because the proposal would benefit manufacturers regardless of size and impose no additional costs, the agency certifies that this rule will not have a significant adverse economic impact on a substantial number of small entities.

VII. Paperwork Reduction Act of 1995

This proposed rule contains collections of information that are subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). ''Collection of information'' includes any request or requirement that persons obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The title, description, and respondent description of the information collection are shown under this section VII with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of

the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Supplements and Other Changes to an Approved Application.

Description: The proposed rule would implement the manufacturing changes provision of section 116 of the Modernization Act and require manufacturers to validate the effect of any manufacturing change on the identity, strength, quality, purity, and potency of a drug or biological product as those factors relate to the safety or effectiveness of the product. The respondent would report the change to FDA in one of the following ways depending on the potential for the change to have an adverse effect on the safety or effectiveness of the product: (1) Changes that have a substantial potential to have an adverse effect on a product would be submitted in a supplement requiring prior approval by FDA before distribution of the product made using the change; (2) changes that have a moderate potential to have an adverse effect on a product would be submitted to FDA in a supplement not less than 30 days prior to distribution of the product made using the change; (3) changes that have a moderate potential to have an adverse effect on a product would be submitted to FDA in a supplement at the time of distribution of the product made using the change ; and (4) changes that have a minimal potential to have an adverse effect on a product would be documented by the respondent in the next annual report.

Proposed §§ 314.70(a)(2) and 601.12(a)(2) would require the holder of an approved application to validate the effects of a manufacturing change on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with the change. This proposed requirement implements the statutory requirement for information collection under section 506A(a) and (b) of the act and, therefore, no burden estimate has been calculated for this regulation.

Proposed §§ 314.70(a)(4) and 601.12(a)(4) would require the applicant to promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented. The transmittal to FDA of advertisements and promotional labeling for drugs and biologics is

accompanied by Form FDA 2253 and regulated by §§ 314.81(b)(3)(i) and 601.12(f)(4). This information collection is approved by OMB until August 31, 2001, under OMB control number 0910–0376. Therefore, this requirement is not estimated in Table 1 of this document.

Proposed § 314.70(a)(5) would require that the applicant include in each supplement (except for a supplement providing for a change in the labeling) a statement certifying that a field copy of the supplement has been provided to the applicant's home FDA district office. Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 4,278 certifications and field copies will be submitted annually as required by proposed § 314.70(a)(5). FDA estimates that approximately 594 applicants will submit these certifications and field copies. Preparation of a field copy would involve copying material already prepared for the supplement, and FDA estimates that it will take an average of 1 hour for applicants to include an additional field copy for FDA.

Proposed §§ 314.70(a)(6) and 601.12(a)(5) would require the applicant to include in the cover letter a list of all changes contained in the supplement or annual report. Based on data concerning the number of supplements and annual reports received by the agency, FDA estimates that approximately 11,913 lists of all changes in the supplement or annual report will be submitted annually as required by proposed § 314.70(a)(6). FDA estimates that approximately 704 applicants will submit these lists. Because the information required would be generated in preparing the supplement or annual report, the agency estimates that, under proposed § 314.70(a)(6), it will take approximately 1 hour to include a list of changes in a cover letter for a supplement or an annual report. FDA estimates that approximately 2,983 lists of all changes in the supplement or annual report will be submitted annually as required by proposed § 601.12(a)(5). FDA estimates that approximately 190 applicants will submit these lists. Because the information required would be generated in preparing the supplement or annual report, the agency estimates that, under proposed § 601.12(a)(5), it will take approximately 1 hour to include a list of changes in a cover letter for a supplement or an annual report.

Proposed § 314.70(b) and current § 601.12(b) set forth requirements for changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). Proposed § 314.70(b)(1) and current § 601.12(b)(1) state that a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product.

Under proposed § 314.70(b)(3) and current § 601.12(b)(3), the applicant must obtain approval of a supplement from FDA prior to distribution of a product made using the change, and the following must be contained in the supplement: (i) A detailed description of the proposed change; (ii) The product(s) involved; (iii) The manufacturing site(s) or area(s) affected; (iv) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validating the effects of the change); (v) The data derived from such studies; (vi) For a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody, relevant validation protocols must be provided; (vii) For sterilization process and test methodologies, relevant validation protocols must be provided; and (viii) A reference list of relevant standard operating procedures when applicable.

The changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes) are listed in proposed § 314.70(b)(2) and current § 601.12(b)(2) (including proposed § 601.12(b)(2)(i)): (i) Changes in the qualitative or quantitative formulation of the drug, including inactive ingredients, or in the specifications provided in the approved application; (ii) Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate the equivalence of the drug to the drug as manufactured without the change or to the reference listed drug; (iii) Changes that may affect product sterility assurance, such as

changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation; (iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance; (v) Certain changes in labeling; (vi) Changes in a container closure system that controls drug delivery or that may affect the impurity profile of the drug product; (vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody for the following: (A) Changes in the virus or adventitious agent removal or inactivation method(s); (B) Changes in the source material or cell line; and (C) Establishment of a new master cell bank or seed; (viii) Changes to a product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application.

Under proposed §§ 314.70(b)(4) and 601.12(b)(4), an applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be marked: ''Prior Approval Supplement-Expedited Review Requested.''

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 1,744 supplements will be submitted annually under proposed § 314.70(b)(1) and (b)(3). FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 80 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 903 supplements are submitted annually under § 601.12(b)(1) and (b)(3). FDA estimates that approximately 190 applicants submit such supplements, and that it takes approximately 80 hours to prepare and submit to FDA each supplement. The burden for an applicant's request, under proposed §§ 314.70(b)(4) and 601.12(b)(4), for FDA to expedite its review of a supplement is negligible and has not been estimated in Table 1 of this document.

Proposed § 314.70(c) and current § 601.12(c) set forth requirements for changes requiring supplement submission at least 30 days prior to distribution of the product made using the change

(moderate changes). Proposed § 314.70(c)(1) and current § 601.12(c)(1) state that a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. Under proposed § 314.70(c)(1), the applicant must submit 12 copies of final printed labeling for all labeling changes.

Under proposed § 314.70(c)(3) and current § 601.12(c)(1), the supplement must set forth a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled ''Supplement—Changes Being Effected in 30 Days.'' Under proposed § 314.70(c)(4) and current § 601.12(c)(3), distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed previously for proposed § 314.70(b)(3) and current § 601.12(b)(3) must be contained in the supplement.

The changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes) are listed in proposed § 314.70(c)(2) (the changes in § 314.70(c)(2)(ii)(A) and (c)(2)(ii)(B) are also listed in current § 601.12(c)(2)): (i) A change in the container closure system that does not affect the quality of the final drug product; and (ii) Changes solely affecting a natural protein product, a recombinant DNA-derived protein/ polypeptide product or a complex or conjugate of a drug with a monoclonal antibody, including: (A) An increase or decrease in production scale during finishing steps that involves new or different equipment; and (B) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 2,754 supplements will be submitted annually under proposed § 314.70(c)(1), (c)(3), and (c)(4). FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 50 hours to prepare and submit to FDA each supplement. FDA

estimates that approximately 255 supplements are submitted annually under § 601.12(c)(1) and (c)(3). FDA estimates that approximately 98 applicants submit such supplements, and that it takes approximately 50 hours to prepare and submit to FDA each supplement.

Under proposed § 314.70(c)(6) and current § 601.12(c)(5), FDA may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug upon receipt by the agency of a supplement for the change. These changes include: (i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess; (ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of product or from one container closure system to another; (iii) Changes in the labeling to accomplish any of the following: (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction; (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage; (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product; (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or (E) Any other changes specifically requested by FDA. Under proposed § 314.70(c)(3) and current § 601.12(c)(1), the supplement must be labeled ''Supplement—Changes Being Effected.''

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 486 supplements will be submitted annually under proposed § 314.70(c)(6). FDA estimates that approximately 486 applicants will submit such supplements, and that it will take approximately 50 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 47 supplements are submitted annually under § 601.12(c)(5). FDA estimates that approximately 34 applicants submit such supplements, and that it takes approximately 50 hours to prepare and submit to FDA each supplement.

Proposed § 314.70(d) and current § 601.12(d) set forth requirements for changes to be described in an annual report (minor changes). Proposed § 314.70(d)(1) and current § 601.12(d)(1) state that changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product must be documented by the applicant in the next annual report.

Under proposed § 314.70(d)(3) and current § 601.12(d)(3) (including proposed § 601.12(d)(3)(iii)), the applicant must submit in the annual report a list of all products involved; and (i) A statement by the holder of the approved application that the effects of the change have been validated; (ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved; and (iii) The date each change was made, a cross-reference to relevant validation protocols and/or SOP's, and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validation).

The changes to be described in an annual report (minor changes) are listed in proposed § 314.70(d)(2) and current § 601.12(d)(2) (including proposed § 601.12(d)(2)(i) through (d)(2)(v) and (d)(2)(vii)): (i) Any change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess; (ii) The deletion or reduction of an ingredient intended to affect only the color of the product; (iii) Replacement of equipment with that of the same design and operating principles except for equipment used with a natural protein product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody; (iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form, without a change from one container closure system to another; (v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency

to the approved system under a protocol approved in the application or published in an official compendium; (vi) An extension of an expiration dating period based upon full shelf-life data obtained from a protocol approved in the application; (vii) The addition, deletion, or revision of an alternate analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application; (viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint; (ix) A change in the labeling concerning the description of the drug product or in the information about how the drug is supplied, that does not involve a change in the dosage strength or dosage form; and (x) An editorial or similar minor change in labeling.

Based on data concerning the number of supplements and annual reports received by the agency, FDA estimates that approximately 6,929 annual reports will include documentation of certain manufacturing changes as required under proposed § 314.70(d)(1) and (d)(3). FDA estimates that approximately 704 applicants will submit such information, and that it will take approximately 10 hours to prepare and submit to FDA the information for each annual report. FDA estimates that approximately 227 annual reports include documentation of certain manufacturing changes as required under current § 601.12(d)(1) and (d)(3). FDA estimates that approximately 166 applicants submit such information, and that it takes approximately 10 hours to prepare and submit to FDA the information for each annual report. Proposed § 314.70(d)(3) and current § 601.12(d)(3) require a statement by the applicant that the effects of the change have been validated. This information is developed by the applicant to validate the effects of the change regarding identity, strength, quality, purity, and potency, and is expressly required to be submitted under section 506A(d)(3)(A) of the act. Therefore, the burden associated with such collection of information is not included in the estimates of Table 1 of this document.

The proposed regulation would reduce the overall number of manufacturing changes subject to supplements, particularly those requiring FDA approval prior to product distribution. Many changes that are currently reported in supplements would be reported in annual reports. Supplement submissions contain more burdensome reporting requirements than a submission through an annual report. The proposed regulation would not increase the number of annual reports but would allow applicants to include in an annual report information currently required to be reported to the agency in a supplemental application. The number of manufacturing changes currently reported in supplements that would be reported in annual reports is approximately 1,283.

Proposed § 314.70(e) and current § 601.12(e) state that an applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Any such protocols, or changes to a protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 50 protocols will be submitted annually under proposed § 314.70(e). FDA estimates that approximately 50 applicants will submit such protocols, and that it will take approximately 20 hours to prepare and submit to FDA each protocol. FDA estimates that approximately 20 protocols are submitted annually under § 601.12(e). FDA estimates that approximately 14 applicants submit such protocols, and that it takes approximately 20 hours to prepare and submit to FDA each protocol.

Current § 601.12(f) sets forth the requirements for supplement submission for labeling changes for biological products. Current § 601.12(f)(2)(i)(A) through (f)(2)(i)(D) specify those labeling

changes for which an applicant must submit a supplement to FDA at the time the change is made. Proposed § 601.12(f)(2)(i)(E) would add ''any other changes specifically requested by FDA'' to these types of changes. FDA estimates that approximately 12 labeling supplements are submitted annually under current § 601.12(f)(1). FDA estimates that approximately 12 applicants submit these supplements, and that it takes approximately 40 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 10 labeling supplements are submitted annually under current § 601.12(f)(2), including those that would be submitted under proposed § 601.12(f)(2)(i)(E). FDA estimates that approximately 10 applicants submit these supplements, and that it takes approximately 20 hours to prepare and submit to FDA each supplement. FDA estimates that approximately 100 annual reports for labeling changes are submitted under current § 601.12(f)(3). FDA estimates that approximately 70 applicants submit these reports, and that it takes approximately 10 hours to prepare and submit to FDA each report. FDA estimates that approximately 1,495 labeling supplements are submitted annually under current § 601.12(f)(4). FDA estimates that approximately 61 applicants submit these supplements, and that it takes approximately 10 hours to prepare and submit to FDA each supplement.

Proposed § 314.70(f) states that an applicant must comply with the patent information requirements under section 505(c)(2) of the act. Proposed § 314.70(g) states that an applicant must include any applicable exclusivity information with a supplement as required under § 314.50(j). Patent and exclusivity information collection requirements are approved by OMB until May 31, 2001, under OMB control number 0910–0305. Therefore, this requirement is not estimated in Table 1 of this document.

Description of Respondents: Business or other for-profit organizations.

In compliance with section 3507(d) of the PRA (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for its review and approval of these information collections. Interested persons are requested to send comments regarding this collection of information, including suggestions for reducing this burden, to the Office of Information and Regulatory Affairs,

OMB (address above), Attn: Wendy Taylor, Desk Officer for FDA. Submit written comments on the collection of information by (*insert date 30 days after date of publication in the* **Federal Register**).

TABLE 1.—Estimated Annual Reporting Burden[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
314.70(a)(5)	594	7	4,278	1	4,278
314.70(a)(6)	704	17	11,913	1	11,913
314.70(b)(1) and (b)(3)	594	3	1,744	80	139,520
314.70(c)(1), (c)(3), and (c)(4)	594	5	2,754	50	137,700
314.70(c)(6)	486	1	486	50	24,300
314.70(d)(1) and (d)(3)	704	10	6,929	10	69,290
314.70(e)	50	1	50	20	1,000
601.12(a)(5)	190	16	2,983	1	2,983
601.12(b)(1) and (b)(3)	190	5	903	80	72,240
601.12(c)(1) and (c)(3)	98	3	255	50	12,750
601.12(c)(5)	34	1	47	50	2,350
601.12(d)(1) and (d)(3)	166	1	227	10	2,270
601.12(e)	14	1	20	20	400
601.12(f)(1)	12	1	12	40	480
601.12(f)(2)	10	1	10	20	200
601.12(f)(3)	70	1	100	10	1,000
601.12(f)(4)	61	25	1,495	10	14,950
Total					497,624

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Request for Comments

Interested persons may, on or before (*insert date 75 days after date of publication in the* **Federal Register**), submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Submit written comments on the information collection requirements as described in paragraph VII of this document by (*insert date 30 days after date of publication in the* **Federal Register**).

List of Subjects

21 CFR Part 5

Authority delegations (Government agencies), Imports, Organization and functions (Government agencies).

21 CFR Parts 206 and 250

Drugs.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 5, 206, 250, 314, 600, and 601 be amended as follows:

PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION

1. The authority citation for 21 CFR part 5 continues to read as follows:

Authority: 5 U.S.C. 504, 552, App. 2; 7 U.S.C. 138a, 2271; 15 U.S.C. 638, 1261–1282, 3701–3711a; 15 U.S.C. 1451–1461; 21 U.S.C. 41–50, 61–63, 141–149, 321–394, 467f, 679(b), 801–886, 1031–1309; 35 U.S.C. 156; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 264, 265, 300u–300u–5, 300aa–1; 1395y, 3246b, 4332, 4831(a), 10007–10008, E.O. 11921, 41 FR 24294, 3 CFR, 1977 Comp., p. 124–131; E.O. 12591, 52 FR 13414, 3 CFR, 1988 Comp., p. 220–223.

§ 5.80 [Amended]

2. Section 5.80 *Approval of new drug applications and their supplements* is amended in the first sentence of paragraphs (d) and (f) by removing the phrase ''§§ 314.70(b)(1), (b)(2)(ii) through (b)(2)(x), (c)(1), and (c)(3)'' and by adding in its place the phrase ''§ 314.70(b)(1), (b)(2)(i) excluding changes in qualitative or quantitative formulation, (b)(2)(iii), (b)(2)(iv), (b)(2)(vi), (b)(2)(vii), (c)(2)(i), (c)(2)(ii), (c)(6)(i), and (c)(6)(ii)''; and in the first sentence of paragraph (e) by removing the phrase ''§§ 314.70(b)(3) and (c)(2)(i) through (c)(2)(iv)'' and by adding in its place the phrase ''§ 314.70(b)(2)(v) and (c)(6)(iii)''.

PART 206—IMPRINTING OF SOLID ORAL DOSAGE FORM DRUG PRODUCTS FOR HUMAN USE

3. The authority citation for 21 CFR part 206 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 371; 42 U.S.C. 262.

§ 206.10 [Amended]

4. Section 206.10 *Code imprint required* is amended in the first sentence of paragraph (b) by removing the phrase ''§ 314.70(b)(2)(xi) or (b)(2)(xii)'' and by adding in its place the phrase ''§ 314.70(b)''.

PART 250—SPECIAL REQUIREMENTS FOR SPECIFIC HUMAN DRUGS

5. The authority citation for 21 CFR part 250 continues to read as follows:

Authority: 21 U.S.C. 321, 336, 342, 352, 353, 355, 361(a), 362(a) and (c), 371, 375(b).

§ 250.250 [Amended]

6. Section 250.250 *Hexachlorophene, as a component of drug and cosmetic products* is amended in the last sentence of paragraph (c)(4)(ii) by removing the phrase ''§ 314.70(c)(2)'' and by adding in its place the phrase ''§ 314.70(c)(6)(iii)''.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

7. The authority citation for 21 CFR part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356a, 371, 374, 379e.

8. Section 314.3 is amended in paragraph (b) by alphabetically adding the definitions for ''Specification'' and ''Validate the effects of the change'' to read as follows:

§ 314.3 Definitions.

* * * * *

(b) * * *

Specification means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials. For the purpose of this definition, *acceptance criteria* means numerical limits, ranges, or other criteria for the tests described.

* * * * *

Validate the effects of the change means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

9. Section 314.50 is amended in paragraph (d)(1)(ii)(*b*) by removing the phrase ''specifications and test procedures'' and by adding in its place the word ''specification''; in paragraph (d)(1)(v) by removing the phrase ''Except for a foreign applicant, the'' and by adding in its place the word ''The''; in paragraph (d)(3)(i) by adding the word ''procedures'' after the word ''analytical''; in paragraph (d)(3)(ii) by removing the phrases ''specifications or analytical methods'' and ''specification or analytical methods'' each time they appear and by adding in their places the phrase ''tests, analytical procedures, and acceptance criteria''; in paragraph (d)(4)(iv) by removing

the word ''methods'' and by adding in its place the word ''procedures''; in the last sentence of paragraph (e)(1) introductory text and in the first sentence of paragraph (e)(2)(i) by removing the word ''methods'' each time it appears and by adding in its place the word ''procedures''; and by revising the first two sentences of paragraphs (d)(1)(i) and (d)(1)(ii)(*a*) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(1) * * *

(i) *Drug substance.* A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, and analytical procedures. * * *

(ii)(*a*) *Drug product.* A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the composition of the drug product; the specifications for each component; the name and address of each manufacturer of the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, containers and closure systems; and stability data with proposed expiration dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative

components, manufacturing and packaging procedures, in-process controls, and analytical procedures. * * *

* * * * *

§ 314.60 [Amended]

10. Section 314.60 *Amendments to an unapproved application* is amended in paragraph (c) by removing the phrase '', other than a foreign applicant,''.

11. Section 314.70 is revised to read as follows:

§ 314.70 Supplements and other changes to an approved application.

(a) *Changes to an approved application.* (1) The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant shall notify FDA about it in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

(2) The holder of an approved application under section 505 of the act shall validate the effects of the change on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant shall make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant shall promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with this section.

(5) Except for a supplement providing for a change in the labeling, the applicant shall include in each supplemental application providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy of the supplement has been provided to the applicant's home FDA district office.

(6) A supplement or annual report shall include in the cover letter a list of all changes contained in the supplement or annual report.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).* (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product.

(2) These changes include, but are not limited to:

(i) Except as provided in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug, including inactive ingredients, or in the specifications provided in the approved application;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug to the drug as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(vi) Changes in a container closure system that controls drug delivery or that may affect the impurity profile of the drug product;

(vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/ polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following shall be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validating the effects of the change);

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody, relevant validation protocols shall be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies, relevant validation protocols shall be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(viii) A reference list of relevant standard operating procedures (SOP's) when applicable.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on

the applicant. Such a supplement and its mailing cover should be plainly marked: ''Prior Approval Supplement-Expedited Review Requested.''

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).* (1) A supplement shall be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. If the change concerns labeling, include 12 copies of final printed labeling.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the final drug product; and

(ii) Changes solely affecting a natural protein product, a recombinant DNA-derived protein/ polypeptide product or a complex or conjugate of a drug with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves new or different equipment; and

(B) Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement shall be labeled ''Supplement—Changes Being Effected in 30 Days'' or, if applicable under paragraph (c)(6) of this section, ''Supplement—Changes Being Effected.''

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(viii) of this section shall be contained in the supplement.

(5) The applicant shall not distribute the product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant shall not distribute the product made using the change until FDA determines that compliance with this section is achieved.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of product or from one container closure system to another;

(iii) Changes in the labeling to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any other changes specifically requested by FDA.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug products made with the manufacturing change.

(d) *Changes to be described in an annual report (minor changes).* (1) Changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product shall be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

(2) These changes include, but are not limited to:

(i) Any change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) The deletion or reduction of an ingredient intended to affect only the color of the product;

(iii) Replacement of equipment with that of the same design and operating principles except for equipment used with a natural protein product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody;

(iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form, without a change from one container closure system to another;

(v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(vi) An extension of an expiration dating period based upon full shelf life data on full production batches obtained from a protocol approved in the application;

(vii) The addition, deletion, or revision of an alternate analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application;

(viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;

(ix) A change in the labeling concerning the description of the drug product or in the information about how the drug is supplied, that does not involve a change in the dosage strength or dosage form; and

(x) An editorial or similar minor change in labeling.

(3) For changes under this category, the applicant is required to submit in the annual report a list of all products involved; and

(i) A statement by the holder of the approved application that the effects of the change have been validated;

(ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved; and

(iii) The date each change was made, a cross-reference to relevant validation protocols and/ or SOP's, and relevant data from studies and tests performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product (validation).

(e) *Protocols*. An applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Any such protocols, or changes to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of a drug produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) *Patent information*. The applicant shall comply with the patent information requirements under section 505(c)(2) of the act.

(g) *Claimed exclusivity*. If an applicant claims exclusivity under § 314.108 upon approval of a supplement for change to its previously approved drug product, the applicant shall include with its supplement the information required under § 314.50(j).

§ 314.81 [Amended]

12. Section 314.81 *Other postmarketing reports* is amended in paragraph (b)(1)(ii) by removing the word ''specifications'' and by adding in its place the word ''specification''.

§ 314.94 [Amended]

13. Section 314.94 *Content and format of an abbreviated application* is amended in the second sentence of paragraph (d)(2) by removing the word ''methods'' each time it appears and by adding in its place the word ''procedures''.

§ 314.410 [Amended]

14. Section 314.410 *Imports and exports of new drugs* is amended in paragraph (b)(2) by removing the word ''specifications'' and by adding in its place the word ''specification''.

§ 314.430 [Amended]

15. Section 314.430 *Availability for public disclosure of data and information in an application or abbreviated application* is amended in paragraph (e)(6) by removing the word ''method'' and by adding in its place the word ''procedure''.

PART 600—BIOLOGICAL PRODUCTS: GENERAL

16. The authority citation for 21 CFR part 600 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 356a, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

17. Section 600.3 is amended by adding paragraphs (hh) and (ii) to read as follows:

§ 600.3 Definitions.

* * * * *

(hh) *Specification*, as used in § 601.12 of this chapter, means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials. For the purpose of this definition, *acceptance criteria* means numerical limits, ranges, or other criteria for the tests described.

(ii) *Validate the effects of the change*, as used in § 601.12 of this chapter, means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

PART 601—LICENSING

18. The authority citation for 21 CFR part 601 is revised to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356a, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263.

19. Section 601.12 is amended by revising paragraphs (a), (b)(2)(i), (d)(2)(i) through (d)(2)(v), and (d)(2)(vii); by adding paragraph (b)(4), (c)(6), (d)(3)(iii), and (f)(2)(i)(E); and by removing and reserving paragraph (c)(2)(i) to read as follows:

§ 601.12 Changes to an approved application.

(a) *General.* (1) As provided by this section, an applicant shall inform the Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s).

(2) Before distributing a product made using a change, an applicant shall validate the effects of the change and demonstrate through appropriate validation and/or other clinical and/or

nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

(3) Notwithstanding the requirements of paragraphs (b), (c), and (f) of this section, an applicant shall make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant shall promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with this section.

(5) A supplement or annual report shall include in the cover letter a list of all changes contained in the supplement or annual report.

(b) * * *

(2) * * *

(i) Except as provided in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation, including inactive ingredients, or in the specifications provided in the approved application;

* * * * *

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement-Expedited Review Requested."

(c) * * *

(2) * * *

(i) [Reserved]

* * * * *

(6) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the products made with the manufacturing change.

(d) * * *

(2) * * *

(i) Any change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) The deletion or reduction of an ingredient intended only to affect the color of the product, except that a change intended only to affect Blood Grouping Reagents requires supplement submission and approval prior to distribution of the product made using the change in accordance with the requirements set forth in paragraph (b) of this section;

(iii) An extension of an expiration dating period based upon full shelf life data on full production batches obtained from a protocol approved in the application;

(iv) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(v) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form, without a change from one container closure system to another;

* * * * *

(vii) The addition, deletion, or revision of an alternate analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

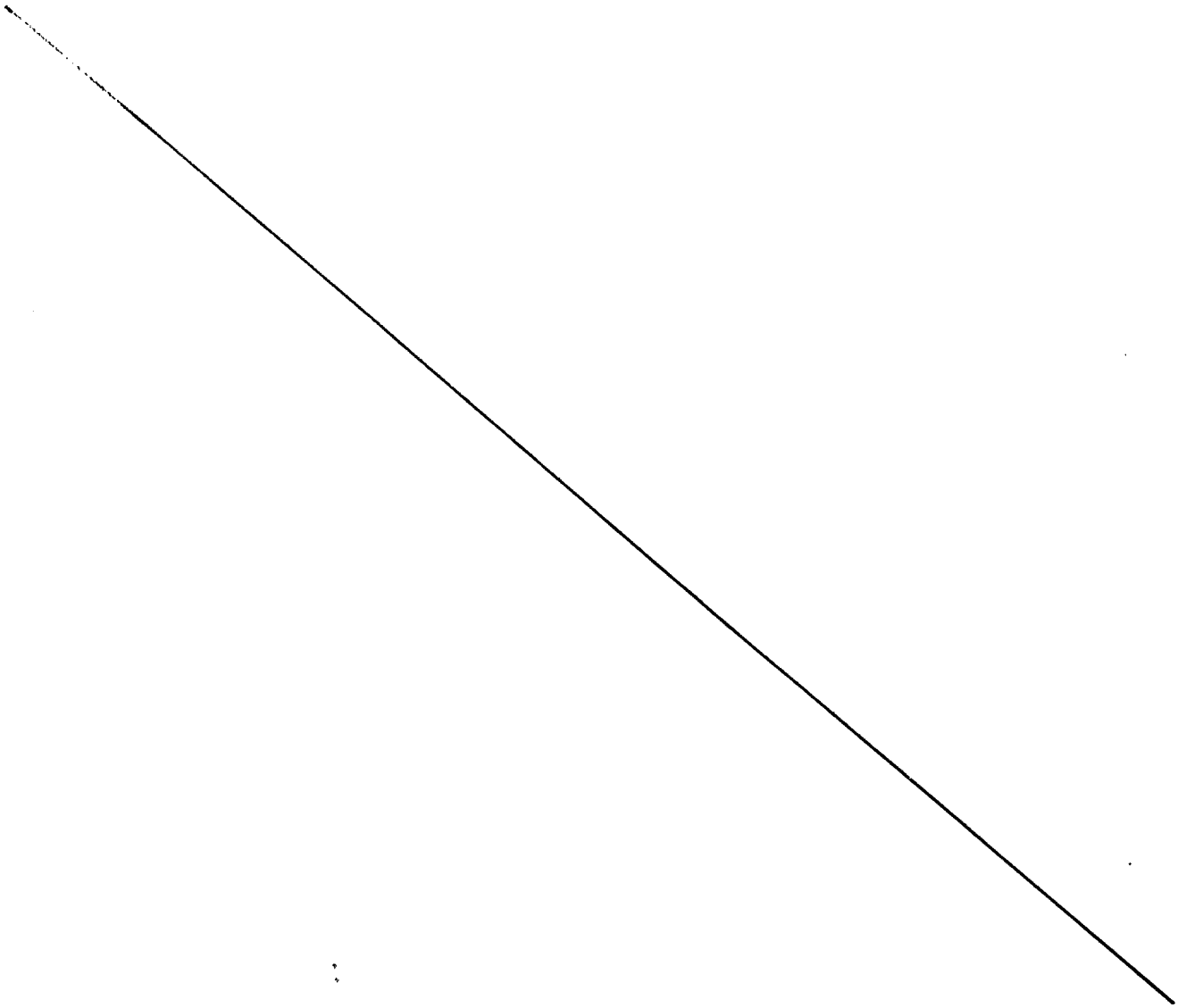
(3) * * *

(iii) A statement by the holder of the approved application or license that the effects of the change have been validated.

* * * * *

(f) * * *

(2) * * *



(i) * * *

(E) Any other changes specifically requested by FDA.

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Dated: June 18, 1999

William K. Hubbard
Acting Deputy Commissioner for
Policy

[FR Doc. 99–???? Filed ??–??–99; 8:45 am]

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